REMARKS

FORMAL MATTERS:

Claims 1-21, 26-30 and 35-43 are pending after entry of the amendments set forth herein.

Claims 3-6, and 29 are pending, but are withdrawn as being directed to a non-elected species.

Claims 22-25, 31-34 are canceled without prejudice. Applicants expressly reserve the right to pursue subject matter of the canceled claims in a continuing application.

Claims 1-21, and 26-30 are amended. Support for these amendments is found throughout the specification. For example, support for the amendments to claim 1 is found in the claim as originally filed, as well as at

- page 5, lines 14-23; page 7, line 19 to page 9, line 14; page 10, line 7 and lines 23-28; original claims 2-6 ("microbial"); and
- page 31, lines 18-24 (DNA polymerase activity); page 38, lines 6-15 (nucleoside incorporation and protease activity); page 42, lines 23-28 (RNA polymerase activity); page 48, lines 1-13 (phosphatase activity); page 51, lines 13-20 (gyrase and DNA cleavage activity); page 54, lines 5-13 (CO complex formation) ("functional activity").

Support the amendments to claims 2-21 and 26-30 is found in the claims as originally filed. Amendments to these claims so that the claim language conforms to that of claim 1 find support as exemplified above for claim 1. Additional support for claim amendments is found in, for example, the specification at page 12, line 25 (drug sensitivity or resistance); page 26, line 27 to page 27, line 1 (dosage ranges of compound); and page 4, lines 8-9 (primer sequences).

New claims 35-43 are added. Support for these new claims is found in, for example, original claims 1, 2-6, 9, 10, 26, 28, 20, and 30, as well as in the specification as exemplified above for amendments to claim 1 and at, for example, paragraphs [0012] and [0063].

No new matter is added.

INFORMATION DISCLOSURE STATEMENT (IDS)

An IDS, including an SB/08A form, is submitted with this amendment. Applicants respectfully request that the Examiner initial and return this SB/08A form, thereby indicating that the references cited in the IDS have been reviewed and made of record.

INTERVIEW SUMMARY

Applicants wish to extend their gratitude to Examiner Hill and Examiner Housel for the in-person interview conducted with the undersigned on October 19, 2004.

The rejections of the claims under §101 (utility), §112, ¶2, §112, ¶1 (enablement and written description), §102 and §103. The amendments and arguments set out in the present communication were discussed.

The Examiners agreed that the present amendment avoided the rejections under §101, and §112, ¶2, as well as the rejections §112, ¶1 for enablement and written description.

REJECTIONS UNDER §112, ¶2

Claims 1, 2, 7-21, 26-28 and 30 were variously rejected as being indefinite. Each aspect of this rejection is addressed below.

The bioactive molecule and completeness of method

The Office Action remarks that "it is not clear what the bioactive molecule is."[1] The Office Action also remarks that claim 1 is "not a complete method."[2]

The Examiner kindly suggested that the preamble be changed to recite "evaluating the phenotype" in the preamble and that reference be made to a "produced" bioactive molecule.

Applicants have incorporated the Examiner's suggestions. Applicants respectfully submit that the amendments to the claims address this rejection.

"Bioactive molecules further comprising"

Claims 7-9 were rejected for recitation of "a bioactive molecule further comprising". This rejection has been addressed by amendment of these claims.

Conclusion

In view of the amendments and remarks above, withdrawal of the rejections of the claims under §112, ¶2 is respectfully requested.

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[1] Office Action, April 22, 2004, page 2.

[2] *Id.*

REJECTIONS UNDER §112, ¶1 (ENABLEMENT AND WRITTEN DESCRIPTION) AND §101 (UTILITY)

Claims 1, 2, 7-21, 25-28 and 30 were rejected under §112, ¶1 for lack of a enabling disclosure (Office Action pages 3-5) and lack of written description (Office Action pages 5-6). The claims were also rejected under §101 for lack of utility on the grounds the disclosed invention is inoperative (Office Action page 7). The grounds for each of these rejections are similar.

With respect to enablement, the Office Action states "the specification, while being enabling for detecting the phenotype of a viral polymerase . . . does not reasonably provide enablement for all disease states and bioactive compounds associated with those disease states."[3]

With respect to written description, the Office Action states "The burden of the written description requirement in this application for assaying for phenotype of bioactive molecules for all disease states has not been met. The written description in this case only sets forth screening of viral polymerases."[4]

With respect to utility the Office Action states "The definition of bioactive includes virtually everything . . ."[5]

Each of the enablement, written description and utility rejections are respectfully traversed as applied and as they may be applied to the pending claims.

Enablement and Written Description

The pending claims recite a "microbial bioactive molecule". A disease state associated with such microbial bioactive molecules would thus be a disease state associated with infection by a microbe. The specification as filed describes many examples of such microbial bioactive molecules, including bioactive molecules from viral, bacterial, fungal and protozoal microbes (see, e.g., the specification at page 5, lines 14-23; page 7, line 19 to page 9, line 14; page 10, line 7 and lines 23-28). Thus the specification provides both enablement and written description support for "microbial bioactive molecule".

The specification further provides many examples of assays for detecting a functional activity of such microbial bioactive molecules. Examples provided in the specification include assays for DNA

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[3] *Id.* at page 3.

[4] *Id.* at page 5.

[5] *Id.* at page7/

polymerase activity,[6] nucleoside incorporation and protease activity,[7] RNA polymerase activity[8], phosphatase activity,[9] gyrase and DNA cleavage activity,[10] and CO complex formation.[11] Thus the specification provides both enablement and written description support for assays to assess a phenotype based on a functional activity of a microbial bioactive molecule.

Utility

As to utility, applicant respectfully submit that the claims directed to evaluating a phenotype of a microbial bioactive molecule meet the requirements under §101. As discussed above, the specification provides examples of microbial bioactive molecules, and assays for determining a phenotype based on a functional activity of such molecules.

With respect to the Office Action's note that "bioactive molecule" encompasses both nucleic acids and polypeptides, applicants submit that it is well understood in the art that nucleic acids encompass ribonucleic acids, which can play a role in regulation of expression of a microbial polypeptide. For example, viral RNA often includes an internal ribosomal entry site (IRES), which IRES plays a critical role in expression of viral proteins. Assays that inhibit activity of an IRES in facilitating viral polypeptide translation are contemplated by the present invention, as well as assays in assessing the effect of a compound upon IRES-mediated translation (see specification at, for example, page 41, lines 3-6).

Conclusion

The pending claims, including the newly added claims, recite that the bioactive molecule is a "microbial bioactive molecule". In view of the above remarks and the pending claims, applicants respectfully request withdrawal of all rejections of the claims under §112, ¶1 for enablement and written description, as well as the rejections under §101.

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[6] Specification, page 31, lines 18-24.

[7] Specification, page 38, lines 6-15.

[8] Specification, page 42, lines 23-28.

[9] Specification, page 48, lines 1-13.

[10] Specification, page 51, lines 13-20.

[11] Specification, page 54, lines 5-13.

REJECTIONS UNDER §102

Rejection under §102(a) – Oon (WO 00/18958)

Claims 1, 2, 7-10, 12-16, 19-21, 26, 27 and 30 were rejected as being anticipated by Oon. This rejection is respectfully traversed as applied, and as it may be applied to the pending claims.

Claim 1 recites that the method involves detecting a functional activity of the microbial bioactive molecule. All other rejected claims are dependent upon claim 1, and thus incorporate this limitation. recite

Oon does not teach an assay that measures a functional activity of HBV polymerase. Oon also does not show that the HBV polymerase is functional, i.e., is able to synthesize nucleic acid.

Instead, Oon only discloses a static, competitive binding assay for binding of a nucleotide in the presence of dideoxy nucleotides or lamivudine. Oon refers to this "activity" of the HBV polymerase as a "priming activity", and the effect of dideoxy nucleotides or lamivudine upon this "activity" as an "anti-priming effect". Oon does not demonstrate that the HBV DNA polymerase produced in an in vitro, cell-free assay following transcription and translation exhibits functional activity, i.e., polymerase activity.

Therefore, Oon fails to anticipate the claimed invention.

Claims 35-43 also recite detecting a functional activity of the microbial bioactive molecule, and thus the arguments above apply.

Furthermore, applicants note that that claim 28, which recites use of one or more nested primer sets to amplify the bioactive molecule-encoding nucleic acid, was not rejected as being anticipated by Oon. New claims 35-43 include the limitation of claim 29, and thus are likewise not anticipated by Oon. In addition, new claim 43 indicates that in vitro transcription and translation proceeds without purification of the PCR amplification product of the prior step.

In view of the above, applicants respectfully request withdrawal of this rejection.

Rejection under §102(b) – Larder (Science (1989) 246:1155-1158)

Claims 1, 2, 15, 16, 19-21 and 30 were rejected as being anticipated by Larder. This rejection is respectfully traversed as applied, and as it may be applied to the pending claims.

Larder does not disclose use of a cell-free transcription and translation system.

The pending claims require use of a cell-free in vitro transcription and translation system. Applicants note that cell-free, eukaryotic or prokaryotic transcription and translation systems are recited in claims 10-13, and that none of these claims are rejected as being anticipated by Larder. Thus claim 1 and its dependent claims, as well as new claims 35-40, which also require a cell-free transcription and translation system, are also not anticipated by Larder.

In view of the above, applicants respectfully request withdrawal of this rejection.

REJECTION UNDER §103(A)

Claims 1, 11, 17 and 18 were rejected as being obvious over Larder in view of either the Promega Catalog or the Invitrogen Catalog.

Larder fails to disclose a cell-free transcription and translation system or a purification motif.

The Office Action attempts to fill this gap in Larder by combining Larder with the cell-free transcription and translation systems described in the Promega catalog and the purification motif described in the Invitrogen catalog.

This rejection is respectfully traversed as applied and as it may be applied to the pending claims.

As discussed above, the pending claims require use of a cell-free transcription and translation system.

As set out in MPEP §2143, establishing a *prima facie* case of obviousness requires that three basic criteria be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Applicants respectfully submit that the obviousness rejection based on the combination of Larder with the Promega catalog, or with the Invitrogen catalog, fails to meet each of these three criteria.

Larder in view of the Promega catalog

First, there is no suggestion or motivation in any of the cited references to combine a **cell-based** assay in which reverse transcriptase (RT) is expressed and its enzymatic activity (Larder) with a **cell-free**, in vitro transcription and translation system of the Promega catalog. The Office Action argues that the ordinarily skilled artisan would be motivated to make this combination since "this systems allows for fine mapping, and rapid of verification of *in vitro* generated mutants because the products are not cloned and the expressed product can be analyzed *in vitro*."[12] However, the Promega catalog – as well as the prior art -- fails to provide any suggestion or motivation for adapting a cell-based assay to express a protein **and** assess a functional activity of that protein to an assay that is cell-free for **both** of these aspects.

Second, there is nothing in the combination of the Larder and the Promega catalog that provides a reasonable expectation of success in producing an RT of Larder in a **cell-free system and** assessing enzymatic activity of that RT in the presence of a compound in a *cell free* system. For example, there is nothing in the Promega catalog that indicate enzymatic activity of a protein (such as RT) in presence of a drug (such as zidovudine) can be assessed in a cell-free assay.

Third, the combined references do not provide all the elements of the pending claims. None of the references provide a **cell-free** system for producing a microbial bioactive molecule **and** a cell-free system for assessing a functional activity of the microbial bioactive molecule.

Applicants respectfully submit that the claimed invention is not obvious in view of the combined teachings of Ladner and the Promega catalog, and request withdrawal of this rejection.

Larder in view of the Invitrogen catalog

As to the assertions in the Office Action regarding the use of a purification motif being obvious in view of the combination of Larder and the Invitrogen catalog, applicants respectfully submit that this aspect of the rejection also fail to meet the three criteria required for *prima facie* obviousness. Larder is silent as to the need or desire to purify an RT expressed in the cell-based system described therein. For example, Larder discusses that mutations in RT can be assessed at the nucleotide sequence level to assess the drug resistance/sensitivity. Assessing such mutations at the amino acid sequence level would

[12] Office Action, April 22, 2004, page 10.

be very time consuming. In short, the ordinarily skilled artisan would not be motivated to isolate the RT protein using a purification motif of the Invitrogen catalog based on the teachings of Larder.

Applicants respectfully submit that the claimed invention is not obvious in view of the combined teachings of Ladner and the Invitrogen catalog, and request withdrawal of this rejection.

Comments as to pending claims

Applicants note that none of claims 10, 12 or 13 – which recite use of an *in vitro* eukaryotic transcription and translation system – were rejected as being anticipated by Larder or as being obvious in view of a combination of Larder with the Promega or Invitrogen catalogs. Further, none of claims 26-29 – which recite amplification of the nucleic acid encoding the bioactive molecule – were also rejected as being anticipated by Larder or as being obvious in view of a combination of Larder with the Promega or Invitrogen catalogs.

New claims 35-40 require amplification of a nucleic acid encoding the microbial bioactive molecule, and further dependent claim 41 recites use of a eukaryotic cell-free transcription and translation system. Applicants respectfully submit that these claims are thus allowable over Larder, either alone or in combination with either the Promega or Invitrogen catalogs.

Conclusion

In view of the above, applicants respectfully request withdrawal of the rejection of the claims under §103(a).

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number FOCS-001.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Oct 22, 2004

By: _____
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Enclosure(s): Revocation and New Power of Attorney
Information Disclosure Statement

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